1: Science 1994 Apr 29;264(5159):707-10

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A lymphotoxin-beta-specific receptor.

Crowe PD, VanArsdale TL, Walter BN, Ware CF, Hession C, Ehrenfels B, Browning JL, Din WS, Goodwin RG, Smith CA.

Division of Biomedical Sciences, University of California, Riverside 92521.

Tumor necrosis factor (TNF) and lymphotoxin-alpha (LT-alpha) are members of a family of secreted and cell surface cytokines that participate in the regulation of immune and inflammatory responses. The cell surface form of LT-alpha is assembled during biosynthesis as a heteromeric complex with lymphotoxin-beta (LT-beta), a type II transmembrane protein that is another member of the TNF ligand family. Secreted LT-alpha is a homotrimer that binds to distinct TNF receptors of 60 and 80 kilodaltons; however, these receptors do not recognize the major cell surface LT-alpha-LT-beta complex A receptor specific for human LT-beta was identified, which suggests that cell surface LT may have functions that are distinct from those of secreted LT-alpha.

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Proinflammatory responses are efficiently induced by homotrimeric but not heterotrimeric lymphotoxin ligands.

Hochman PS, Majeau GR, Mackay F, Browning JL.

Biogen, Cambridge, Massachusetts 02142, USA.

The cytokine, lymphotoxin [LT, tumor necrosis factor beta (TNF beta)] is a potent mediator of proinflammatory and tumoricidal activities. Soluble lymphotoxin is a complex of three LT alpha chains. Its receptors, TNF-R55 and TNF-R75, bind in clefts formed by adjacent identical LT alpha monomers. LT also exists as membrane anchored heterotrimers comprised of LT alpha and LT beta chains. The major and minor membrane forms, LT alpha 1 beta 2 and LT alpha 2 beta 1, respectively, bind a unique receptor, LT beta-R. As LT alpha 2 beta 1 expresses an LT alpha-alpha cleft, it also binds TNF-R. In this report we have compared the effects of ligand engagement of TNF-R and LT beta-R by evaluating the ability of soluble LT alpha beta complexes to initiate activities of human umbilical vein endothelial cells which are characteristically signalled by TNF. We recently reported that soluble LT alpha 1 beta 2 signals via LT beta-R to mediate cytotoxicity of a subset of gamma interferon (IFN-gamma) treated carcinomas. We now show that human LT alpha beta heterotrimers do not efficiently activate LT beta-R+, TNF-R+ human endothelial cells in vitro and only inefficiently mediates lethal toxicity in mice. We also show that neither LT alpha beta heterotrimer signals via TNF-R; in fact LT alpha 2 beta 1 trimers fail to activate NF-kappa B and rather inhibit ligand-induced TNF-R signalling supporting the role for aggregation in TNF-R signalling. Thus, the ability of LT alpha beta complexes to efficiently initiate tumoricidal but not inflammatory activities distinguishes the LT/LT beta-R from the LT/TNF-R pathways and suggest novel strategies for exploiting the LT ligands in tumor therapy and for inhibiting TNF-R-mediated inflammatory sequellae.

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